

# The COVID-19 Treatment Guidelines Panel's Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Treatment of COVID-19

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## Background

Tocilizumab is a recombinant humanized anti-interleukin (IL)-6 receptor monoclonal antibody that is approved by the Food and Drug Administration (FDA) for the treatment of certain rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR-T) therapy. Similar agents in this class include sarilumab, which is FDA-approved for the treatment of rheumatoid arthritis. It is hypothesized that modulating the levels of pro-inflammatory IL-6 or its effects may improve the course of COVID-19. To date, no IL-6 inhibitor is FDA-approved or authorized for the treatment of COVID-19.

## Brief Summary of Evidence

Initial studies evaluating the use of IL-6 inhibitors for the treatment of COVID-19 produced conflicting results. Many trials evaluating tocilizumab were limited by low power, heterogeneous study populations with varying degrees of disease severity, and/or low frequency of concomitant use of corticosteroids, which has become the standard of care for patients with severe or critical COVID-19.<sup>1-3</sup> These trials failed to demonstrate a reduction of mortality within 1 month of tocilizumab treatment. However, other trials found that tocilizumab treatment lowered the incidence or duration of intensive care unit (ICU) and hospital stays (A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia [COVACTA])<sup>4</sup> or lowered the composite rate of mechanical ventilation or death (Evaluating Minority Patients With Actemra [EMPACTA]).<sup>5</sup> The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) enrolled critically ill patients requiring respiratory support who were admitted to an ICU. Patients were randomized within 24 hours of ICU admission, and within a median of 1.2 days (IQR 0.8–2.8) of hospitalization. The preliminary report of the REMAP-CAP trial noted that, compared to placebo, the use of either tocilizumab or sarilumab reduced both mortality and time to ICU discharge, and increased the number of organ support-free days.<sup>6</sup> The recommendations of the COVID-19 Treatment Guidelines Panel (the Panel) for tocilizumab and sarilumab are based on the collective evidence from clinical trials that have reported results to date.

### **Based on the available evidence, the Panel has determined the following:**

- For patients who are within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen ( $>0.4 \text{ FiO}_2/30 \text{ L/min}$  of oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19.
- Although many trials of tocilizumab for the treatment of COVID-19 have included patients who meet the above criteria, the collective data available to date preclude a definitive recommendation for or against the use of the drug.
- In view of the results from the REMAP-CAP trial (described below), some Panel members would administer a single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure.

- Too few patients in REMAP-CAP received sarilumab for the Panel to assess its efficacy in the treatment of patients who met the above criteria.
- For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of **tocilizumab** or **sarilumab** for the treatment of COVID-19, except in a clinical trial (**BIIa**).

### **Additional Considerations:**

- Panel members who would administer a single dose of tocilizumab would give the drug in combination with a course of dexamethasone therapy because >80% of the patients enrolled in the REMAP-CAP trial also received corticosteroids, which is consistent with the current standard of care.
- Several trials allowed for a second dose of tocilizumab per discretion of the investigator. Currently, there are insufficient data to support repeated dosing of tocilizumab.
- There were very few immunocompromised patients enrolled in the REMAP-CAP trial; thus, the safety of using a combination of tocilizumab and dexamethasone for these patients is unknown. The risk of superinfection should be considered and monitored for, particularly in the setting of concomitant corticosteroid use.
- There are no data from systematic observational cohorts or randomized controlled trials on the use of IL-6 inhibitors in children for the treatment of acute COVID-19. In children, tocilizumab has been used to treat cytokine release syndrome associated with CAR-T therapy and systemic and polyarticular juvenile idiopathic arthritis.
- Use of tocilizumab for the treatment of COVID-19 may affect supplies for other indications, such as rheumatic diseases and cytokine release syndrome related to CAR-T therapy. Health systems are encouraged to ensure an adequate supply of tocilizumab for patients who need the drug for the FDA-approved indications.
- The collective evidence that led to the Panel's recommendations are based on studies using tocilizumab. The results of randomized controlled trials of sarilumab that are underway will further understanding of the role sarilumab plays in the treatment of COVID-19.
- Sarilumab and tocilizumab have a similar mechanism of action. However, in the REMAP-CAP trial, the number of participants who received sarilumab was relatively small. Moreover, the trial evaluated sarilumab for intravenous administration, which is not the approved formulation in the United States.

## **Clinical Trial Data**

### ***Critically Ill Patients Who Were Admitted to an Intensive Care Unit***

*This study has not been peer reviewed.*

To date, the largest trial that has investigated the use of IL-6 inhibitors in patients with COVID-19 is the REMAP-CAP trial, a multinational, adaptive, randomized controlled trial that randomly assigned 803 participants with suspected or confirmed COVID-19 to receive immune modulation with an IL-6 receptor antagonist (353 participants received tocilizumab and 48 received sarilumab) or the standard of care (402 participants).<sup>6</sup> In a preliminary non-peer reviewed report of outcomes among critically ill patients who were hospitalized for <15 days, and were admitted to an ICU for <24 hours, and required respiratory and/or cardiovascular organ support, the following treatment effects were described:

- Compared to standard of care, one or two doses of tocilizumab decreased in-hospital mortality

(28% of the tocilizumab patients vs. 36% of the standard of care patients died), improved in-hospital survival (aOR 1.64; 95% credible intervals [CrI], 1.14–2.35), and increased the number of organ support-free days (aOR 1.64; 95% CrI, 1.25–2.14).

- Compared to standard of care, one dose of sarilumab (n = 48) decreased in-hospital mortality (22% of the sarilumab patients vs. 36% of the standard of care patients died), improved in-hospital survival (aOR 2.01; 95% CrI, 1.18–4.71), and increased the number of organ support-free days (aOR 1.76; 95% CrI, 1.17–2.91).

The distribution of patients who required respiratory support at baseline included 28.8% requiring high-flow oxygen, 41.5% requiring noninvasive mechanical ventilation, and 29.4% requiring invasive mechanical ventilation. More than 80% of the patients received concomitant corticosteroids. More than 75% of the participants received the IL-6 inhibitors within 3 days of hospital admission, suggesting that the benefit of tocilizumab or sarilumab may occur primarily among patients whose condition is rapidly deteriorating. An assessment of the safety of tocilizumab or sarilumab is limited by the low number of adverse events reported in this trial.

Several other large, well-conducted, randomized controlled trials that included critically ill patients reported mixed results. The reasons for the differences across the trials is uncertain. Possibilities include the varying degree of respiratory dysfunction among the patients enrolled in each study, racial and ethnic differences in the populations studied, differences in the frequency of corticosteroid use (with higher use in the REMAP-CAP and EMPACTA trials), and differences in the use of other co-interventions because the trials were conducted at different times during the pandemic as COVID-19 treatment practice evolved.

### ***Severely Ill Patients Who Require Supplemental Oxygen but Not High-Flow Oxygen, Invasive Mechanical Ventilation, or Admission to an Intensive Care Unit***

The EMPACTA trial randomized patients with severe COVID-19 (n = 389) to tocilizumab or placebo; those who required noninvasive or invasive mechanical ventilation were subsequently excluded from the trial.<sup>5</sup> More than 80% of the participants in the modified intention-to-treat population (n = 377) were members of a racial or ethnic minority group.<sup>5</sup> The primary outcome, a composite of mortality or invasive mechanical ventilation at Day 28, favored tocilizumab over placebo (12.0% in the tocilizumab arm vs. 19.3% in the placebo arm; HR 0.56; 95% CI, 0.33–0.97; *P* = 0.04). However, there was no difference between the arms in all-cause mortality at Day 28.

The COVACTA trial enrolled 452 patients with COVID-19; 69% of the participants required noninvasive or invasive mechanical ventilation.<sup>4</sup> The participants were randomized 2:1 to tocilizumab or placebo. There was no difference between the arms in the primary outcome, clinical status (based on a seven-point ordinal scale) at Day 28 (OR 1.19; 95% CI, 0.81–1.76), or overall mortality. However, results for secondary outcome measures indicated that patients who received tocilizumab had a shorter time to hospital discharge than those who received placebo (20 days in the tocilizumab arm vs. 28 days in the placebo arm; HR 1.35; 95% CI, 1.02–1.79; *P* = 0.04) and a shorter ICU stay (9.8 days in the tocilizumab arm vs. 15.5 days in the placebo arm; *P* = 0.05).

The randomized, controlled, Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial enrolled 243 patients and found no effect on the primary outcome measure, a composite of time to intubation or death at 28 days (HR 0.83; 95% CI, 0.38–1.81; *P* = 0.64).<sup>1</sup> Similarly, the open-label, international CORIMUNO-19–Tocilizumab (CORIMUNO-TOCI-1)<sup>2</sup> and Efficacy of Early Administration of Tocilizumab in COVID-19 Patients (RCT-TCZ-COVID-19)<sup>7</sup> trials did not identify a mortality benefit from tocilizumab in patients with moderate or severe COVID-19 who did not require organ support. These latter trials each had significant methodological limitations, including lack of

blinding, insufficient power, and/or lack of a racially and ethnically diverse cohort.

Recommendation Rating Scheme
<b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional
<b>Rating of Evidence:</b> I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

## References

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